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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 06/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/714,391	GRIFFITHS ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *4,33 and 36-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5-32 and 34-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-41 are pending.

Election/Restrictions

2. Applicant's election with traverse of the invention of Group I claims 2-32 and 34-35 and (B) EGP-1 in the reply filed on 13 March 2006 is acknowledged. The traversal is on the grounds that there is no search burden as all the species are classified in class 424, subclass 155.1. This has been fully considered but is not found persuasive. As stated in the restriction requirement, the inventions are distinct in that inventions (A)-(NN) are all structurally and chemically different, have different modes of operation, different functions and effects and are not disclosed as capable of use together. Further, art on one of inventions (A)-(NN) would not necessarily be art on any of the others. Thus, different searches and different patentability issues are involved in the examination of each group.

Applicant also argues that claims 1-6 and 9-32 are allowable and are generic to all of inventions (A)-(NN). It is noted that claim 4 is specific to invention (G) and not generic. In view of the art applied in the present office action (see below), claims 1-6 and 9-32 are not yet in condition for allowance. Further, it is noted that the restriction among the linked inventions (I-V) is subject to the allowance of the generic linking claim, claim 1. The examiner also acknowledges applicant's remarks regarding rejoinder, however, applicant did not elect claims directed to the product.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 4, 33 and 36-41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

4. Claims 1-3, 5-32 and 34-35 are under examination to the extent that the tumor-associated antigen is EGP-1.

Specification

5. The disclosure is objected to because of the following informalities

Applicant is reminded that the disclosure of US Application serial numbers 10/116,116 and 09/337,756 (see pp. 7 and 11) in the specification should be updated during the pendency of the present application should their status change. It is noted that USSN 10/116,116 is pending and USSN 09/337,756, which is now allowed.

Appropriate correction is required.

Claim Objections

6. Claims 1, 8 and 23 are objected to because of the following informalities:

a. Claims 1 and 8 are objected to as being drawn to non-elected inventions. Claim 1 recites pathogens and claim 8 recites various non-elected tumor-associated antigens.

b. Claims 23 is objected to in the recitation "with an dissociation constant...". Consider revising claim 23 to recite "with a dissociation constant...".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

8. Claim 30 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 30 contains the trademark/trade name TAXOL®. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a sugenus of prodrugs and, accordingly, the identification/description is indefinite.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 1-3, 5, 9-13, 15-16, 24-32, 34-35 are rejected under 35 U.S.C. 102(b) as being anticipated by Hansen et al [a] (WO 99/66951, 12/29/1999).

Claims 1-3, 5, 9-13, 15-16, 24-32, 34-35 are drawn to a method of treating target cells in a mammalian or human subject comprising administering in sequence a non-covalently bound complex to said mammalian or human subject thereby forming a target-tissue localized complex, wherein said non-covalently bound complex comprises a multispecific targeting protein comprising at least one target-binding site and one hapten-binding site, and a hapten-enzyme covalent conjugate, wherein said at least one target-binding site binds to the target cells/tissue and wherein said hapten-binding site is non-covalently bound to the hapten-enzyme covalent conjugate, optionally administering a clearing agent, and administering a chemotherapeutic drug or prodrug, capable of being converted to a more active drug by the target-tissue localized complex and the chemotherapeutic prodrug has greater solubility than the active drug produced by the non-covalently bound complex and the prodrug is a prodrug of a camptothecin, doxorubicin, taxol, actinomycin, maytansine, calicheamicin or epithilone class of drug or is the prodrug CPT-11, a prodrug of SN-38. Further, the multispecific targeting protein is a mutlispecific antibody or multispecific

antibody fragment and is at least bispecific, is multivalent, murine, chimeric, humanized or human and the hapten-enzyme comprises at least one hapten, selected from HSG, DTPA, indium-DTPA, DOTA, indium-DOTA, yttrium-DOTA, fluorescein or biotin and the haptens are linked by a peptide from 2-10, 2-5 or 3 amino acid residues in length and the enzyme of the hapten-enzyme conjugate is an esterase, amidase, glucuronidase, galactosidase or carboxylesterase and the clearing agent is an anti-idiotypic antibody or a galactosylated anti-idiotypic antibody to the multispecific targeting protein.

Hansen et al [a] teach a method of treating a patient comprising administering a bi-specific antibody or fragment having at least one arm that binds a targeted tissue and at least one other arm that binds a hapten and a hapten-enzyme covalent conjugate comprising at least one hapten, wherein the hapten-enzyme conjugate is mixed with the targeting bi-specific antibody prior to administration (i.e., non-covalently bound complex), optionally administering a galactosylated anti-idiotypic antibody (clearing agent) to the bi-specific antibody of the non-covalent complex to clear non-localized non-covalent complexes and administering a chemotherapeutic drug or prodrug that is converted to a more active drug by the pre-targeted enzyme (i.e., target-tissue-localized complex) (see entire document, particularly pp. 4-5, 9-11, 28, lines 20-25, pg. 36, Examples 13-14 and 26). Hansen et al [a] also teach bi-specific or multispecific antibodies and antigen-binding fragments thereof that are monovalent or divalent (pg. 19, lines 14-20), are murine, chimeric, humanized or human antibodies and the hapten-enzyme comprises at least one hapten selected from fluorescein,

DTPA, indium-DTPA, NOTA, DOTA, indium-DOTA and yttrium-DOTA wherein the haptens are linked by a peptide from 2-10 amino acid residues and the enzyme is a glucuronidase or a carboxylesterase, and "can be adopted for use with any enzyme-drug pair" (pg. 30, lines 29-30) according to Hansen et al [a] (see pg. 11-16, 19, 23-24, 29-31, 33-34). Further, Hansen et al [a] teach various prodrugs including epirubicin, topotecan, maytansinoids, calicheamicins and CPT-11, which is converted by carboxylesterase to the active drug SN-38 that remains in the vicinity of the tumor due to its poor solubility, i.e., the prodrug has a greater aqueous solubility than the active drug produced by the non-covalent complex (see pp. 28-30, 33-34).

Thus, Hansen et al [a] anticipate the claims.

11. Claims 1-3, 5, 9-13, 15-16, 24-32, 34-35 are provisionally rejected under 35 U.S.C. 102(e) as being anticipated by copending Application No. 09/337,756; Hansen et al [b] (now allowed) which has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. 102(e), if published under 35 U.S.C. 122(b) or patented. This provisional rejection under 35 U.S.C. 102(e) is based upon a presumption of future publication or patenting of the copending application.

This provisional rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the copending application was derived from the inventor of this

application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131. This rejection may not be overcome by the filing of a terminal disclaimer. See *In re Bartfeld*, 925 F.2d 1450, 17 USPQ2d 1885 (Fed. Cir. 1991).

Hansen et al [b] teach a method of treating a patient comprising administering a bi-specific antibody or fragment having at least one arm that binds a targeted tissue and at least one other arm that binds a hapten and a hapten-enzyme covalent conjugate comprising at least one hapten, wherein the hapten-enzyme conjugate is mixed with the targeting bi-specific antibody prior to administration (i.e., non-covalently bound complex), optionally administering a galactosylated anti-idiotypic antibody (clearing agent) to the bi-specific antibody of the non-covalent complex to clear non-localized non-covalent complexes and administering a chemotherapeutic drug or prodrug that is converted to a more active drug by the pre-targeted enzyme (i.e., target-tissue-localized complex) (see entire document, particularly pp. 4-5, 9-11, 28, lines 20-25, pg. 36, Examples 13-14 and 26). Hansen et al [b] also teach bi-specific or multispecific antibodies and antigen-binding fragments thereof that are monovalent or divalent (pg. 19, lines 14-20), are murine, chimeric, humanized or human antibodies and the hapten-enzyme comprises at least one hapten selected from fluorescein, DTPA, indium-DTPA, NOTA, DOTA, indium-DOTA and yttrium-DOTA wherein the haptens are linked by a peptide from 2-10 amino acid residues and the enzyme is a glucuronidase or a carboxylesterase, and "can be adopted for use with any enzyme-drug pair" (pg. 30, lines 29-30) according to Hansen et al [b]

(see pg. 11-16, 19, 23-24, 29-31, 33-34). Further, Hansen et al teach various prodrugs including epirubicin, topotecan, maytansinoids, calicheamicins and CPT-11, which is converted by carboxylesterase to the active drug SN-38 that remains in the vicinity of the tumor due to its poor solubility, i.e., the prodrug has a greater aqueous solubility than the active drug produced by the non-covalent complex (see pp. 28-30, 33-34).

Thus, Hansen et al [b] anticipate the claims.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any

inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 7-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al [a] (WO 99/66951, 12/29/1999) in view of Basu et al (International Journal of Cancer, 62:472-479, 1995).

Claims 7-8 are drawn to a method of treating EGP-1 expressing tumor cells in a subject comprising administering in sequence a non-covalently bound complex to said subject thereby forming a EGP-1 localized complex, wherein said non-covalently bound complex comprises a multispecific targeting protein comprising at least one EGP-1-binding site and at least one hapten-binding site, and a hapten-enzyme covalent conjugate, optionally administering a clearing agent, and administering a chemotherapeutic drug or prodrug, capable of being converted to a more active drug by the EGP-1 localized complex.

Hansen et al [a] has been described supra. Hansen et al [a] do not specifically teach wherein the bi-specific targeting protein binds EGP-1. This deficiency is made up for in the teachings of Basu et al.

Basu et al teach the epithelial glycoprotein-1 (EGP-1) expressed in various human tumors of epithelial origin including breast, bladder, lung, ovary, prostate, pancreas and stomach and a monoclonal antibody to the EGP-1

antigen, which targets several carcinoma types in patients (see entire document, particularly pg. 472).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced method of treating EGP-1 expressing tumor cells in human patients comprising administering in sequence (i) a non-covalently bound complex comprising a multispecific targeting protein comprising at least one EGP-1-binding site and at least one hapten-binding site, and a hapten-enzyme covalent conjugate, (ii) optionally administering a clearing agent, and (iii) administering a chemotherapeutic drug or prodrug, capable of being converted to a more active drug by the EGP-1 localized complex for therapeutic benefit in human tumor patients.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced method of treating EGP-1 expressing tumor cells in human patients comprising administering in sequence (i) a non-covalently bound complex comprising a multispecific targeting protein comprising at least one EGP-1-binding site and at least one hapten-binding site, and a hapten-enzyme covalent conjugate, (ii) optionally administering a clearing agent, and (iii) administering a chemotherapeutic drug or prodrug, capable of being converted to a more active drug by the EGP-1 localized complex for therapeutic benefit in human tumor patients in view of Hansen et al [a] and Basu et al because Hansen et al [a] teach a method of treating a patient comprising administering a bi-specific antibody or fragment comprising at least one arm that binds a target tissue and at least one

other arm that binds a hapten and a hapten-enzyme covalent conjugate comprising at least one hapten, wherein the hapten-enzyme conjugate is mixed with the targeting bi-specific antibody prior to administration (i.e., non-covalently bound complex), optionally administering a clearing agent to clear unbound non-covalent complexes and administering a chemotherapeutic drug or prodrug that is converted to a more active drug by the pre-targeted enzyme and Basu et al teach the EGP-1 antigen expressed in various human tumors of epithelial origin including breast, bladder, lung, ovary, prostate, pancreas and stomach as well as a monoclonal antibody to the EGP-1 antigen. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to modify the pre-targeting method of Hansen et al [a] to target the human pancarcinoma antigen, EGP-1, for therapeutic benefit in a variety of human tumor patients, and the targetable conjugate (i.e., hapten-enzyme) of Hansen et al [a] provides flexibility in the therapeutic agent without raising new bi-specific antibodies (see pg. 3, lines 18-25). Thus, there would be an advantage to targeting the EGP-1 antigen that is expressed in numerous human tumors, including breast, bladder, lung, ovary, prostate, pancreas and stomach and one of ordinary skill in the art would have a reasonable expectation of success in view of the teachings of Basu et al providing evidence that an EGP-1 antibody targets several carcinoma types in patients. Thus, it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to have produced method of treating EGP-1 expressing tumor cells in human patients comprising administering in sequence (i) a non-covalently bound complex comprising a multispecific targeting protein

comprising at least one EGP-1-binding site and at least one hapten-binding site, and a hapten-enzyme covalent conjugate, (ii) optionally administering a clearing agent, and (iii) administering a chemotherapeutic drug or prodrug, capable of being converted to a more active drug by the EGP-1 localized complex for therapeutic benefit in human tumor patients in view of Hansen et al [a] and Basu et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

14. Claims 6, 10, 14 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al [a] (WO 99/66951, 12/29/1999) in view of Barbet et al (U.S. Patent 5,256,395, issued 10/26/1993) and Haisma et al (Blood, 92(1):184-190, 1998).

Claims 6, 10, 14 and 23 are drawn to a method of treating target cells in a subject comprising administering in sequence a non-covalently bound complex to said human patient thereby forming a target-tissue localized complex, wherein said non-covalently bound complex comprises a multispecific targeting protein comprising at least one target-binding site and one hapten-binding site (i.e., HSG), and a hapten-enzyme covalent conjugate, optionally administering a clearing agent, and administering a chemotherapeutic drug or prodrug, capable of being converted to a more active drug by the target-tissue localized complex, wherein the non-covalently bound complex is injected intravenously, the haptens

are attached via a single reaction site to the enzyme and the bi-specific targeting protein binds to both its antigen target and to its hapten target with a dissociation constant of at least 10^{-7}, more preferably at least 10^{-9}.

Hansen et al [a] has been described supra. Hansen et al [a] do not specifically teach wherein the non-covalently bound complex is injected intravenously, the haptens (i.e., HSG) are attached via a single reaction site to the enzyme and the bi-specific targeting protein binds to both its antigen target and to its hapten target with a dissociation constant of at least 10^{-7}, more preferably at least 10^{-9}. These deficiencies are made up for in the teachings of Barbet et al and Haisma et al.

Barbet et al teach multivalent, multispecific antibodies or antigen-binding fragments thereof comprising two or more binding sites, wherein at least one binding site has affinity towards a hapten moiety (i.e., HSG) and at least one binding site has high affinity towards a tumor-associated antigen and a carrier molecule (affinity enhancement probe) comprising a therapeutic agent and at least two hapten moieties wherein the tumor-associated antigen binding site has a dissociation constant smaller than 10^{-8}M and the hapten binding site has a dissociation constant between 10^{-9}-10^{-7} and is administered by intravenous injection (see entire document, particularly Figures 1-3 and columns 2, 4-5, 6, lines 1-24, col. 8, lines 51-52).

Haisma et al teach that chemical conjugation of enzymes in antibody-directed enzyme prodrug therapy results in conjugate heterogeneity due to the lack of specificity of the reagents used for conjugation and necessitates

additional purification steps and often results in reduced enzymatic activity or diminished binding activity of the conjugate, whereas recombinantly produced conjugates consist of a uniform product with predictable properties (see entire document, particularly, pg. 184, 2nd col. and pg. 188, 2nd col.).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced method of treating tumor cells in a patient comprising administering in sequence (i) a non-covalently bound complex comprising a multispecific targeting protein comprising at least one tumor-binding site and one hapten-binding site, and a hapten-enzyme covalent conjugate, (ii) optionally administering a clearing agent, and (iii) administering a prodrug, capable of being converted to a more active drug by the tumor localized complex for therapeutic benefit in human tumor patients, wherein the non-covalently bound complex is injected intravenously, the haptens are attached via a single reaction site to the enzyme and the bi-specific targeting protein binds to both its antigen target and to its hapten target with a dissociation constant of at least 10^{-7}, more preferably at least 10^{-9}.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced method of treating tumor cells in a patient comprising administering in sequence (i) a non-covalently bound complex comprising a multispecific targeting protein comprising at least one tumor-binding site and one hapten-binding site, and a hapten-enzyme covalent conjugate, (ii) optionally administering a clearing agent, and (iii) administering a prodrug, capable of being converted to a more

active drug by the tumor localized complex for therapeutic benefit in human tumor patients, wherein the non-covalently bound complex is injected intravenously, the haptens are attached via a single reaction site to the enzyme and the bi-specific targeting protein binds to both its antigen target and to its hapten target with a dissociation constant of at least 10^{-7}, more preferably at least 10^{-9} in view of Hansen et al [a] and Barbet et al and Haisma et al because Hansen et al [a] teach a method of treating a patient comprising administering a bi-specific antibody or fragment comprising at least one arm that binds a target tissue and at least one other arm that binds a hapten and a hapten-enzyme covalent conjugate comprising at least one hapten, wherein the hapten-enzyme conjugate is mixed with the targeting bi-specific antibody prior to administration (i.e., non-covalently bound complex), optionally administering a clearing agent to clear unbound non-covalent complexes and administering a chemotherapeutic drug or prodrug that is converted to a more active drug by the pre-targeted enzyme and Barbet et al teach multivalent, multispecific antibodies or antigen-binding fragments thereof comprising two or more binding sites, wherein at least one binding site has affinity towards a hapten moiety including HSG and at least one binding site has high affinity towards a tumor-associated antigen and a carrier molecule (affinity enhancement probe) comprising a therapeutic agent and at least two hapten moieties wherein the tumor-associated antigen binding site has a dissociation constant smaller than 10^{-8}M and the hapten binding site has a dissociation constant between 10^{-9}-10^{-7} and is administered by intravenous injection and Haisma et al teach that chemical conjugation of enzymes in

antibody-directed enzyme prodrug therapy results in conjugate heterogeneity due to the lack of specificity of the reagents used for conjugation and necessitates additional purification steps and often results in reduced enzymatic activity or diminished binding activity of the conjugate, whereas recombinantly produced conjugates consist of a uniform product with predictable properties. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to modify the non-covalent bound complex of Hansen et al [a] to produce a high affinity bi-specific antibody wherein both the tumor-associated antigen and hapten binding sites have a dissociation constant smaller than 10^{-8}M and conjugate the haptens to the enzyme via a single reaction site to produce more uniform enzyme-hapten conjugates with predictable properties avoiding the requirement for further purification steps and reduced enzyme activity associated with conjugate heterogeneity and administer the non-covalent bound complex by intravenous injection in the pre-targeting method of Hansen et al [a]. Thus, there would be advantages to using a high affinity bi-specific antibody and uniform and predictable enzyme-hapten conjugates in the method of Hansen et al [a] for tumor therapy in patients. Thus, it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to have produced method of treating tumor cells in a patient comprising administering in sequence (i) a non-covalently bound complex comprising a multispecific targeting protein comprising at least one tumor-binding site and one hapten-binding site, and a hapten-enzyme covalent conjugate, (ii) optionally administering a clearing agent, and (iii) administering a prodrug, capable of being converted to a more active drug by the

tumor localized complex for therapeutic benefit in human tumor patients, wherein the non-covalently bound complex is injected intravenously, the haptens are attached via a single reaction site to the enzyme and the bi-specific targeting protein binds to both its antigen target and to its hapten target with a dissociation constant of at least 10^{-7}, more preferably at least 10^{-9} in view of Hansen et al [a] and Barbet et al and Haisma et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

15. Claims 17-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al [a] (WO 99/66951, 12/29/1999) in view of Danks et al (Clinical Cancer research 5:917-924, April 1999) and Searle et al (WO 00/43541, published 7/27/2000).

Claims 17-22 are drawn to a method of treating target cells in a subject comprising administering in sequence a non-covalently bound complex to said human patient thereby forming a target-tissue localized complex, wherein said non-covalently bound complex comprises a multispecific targeting protein comprising at least one target-binding site and one hapten-binding site, and a hapten-enzyme covalent conjugate, optionally administering a clearing agent, and administering a chemotherapeutic drug or prodrug, capable of being converted to a more active drug by the target-tissue localized complex, wherein

the enzyme is rat or human carboxylesterase or the enzyme is produced by recombinant techniques in bacteria and is modified by site-directed mutagenesis to enhance its catalytic rate.

Hansen et al [a] have been described supra. Hansen et al [a] do not specifically teach wherein the enzyme is rat or human carboxylesterase or the enzyme is produced by recombinant techniques in bacteria and is modified by site-directed mutagenesis to enhance its catalytic rate. These deficiencies are made up for in the teachings of Dansk et al and Searle.

Danks et al teach rabbit and human carboxylesterases for use in antibody-directed enzyme prodrug therapy of tumor cells, wherein tumor regression occurs in mice bearing xenografts that express rabbit or human carboxylesterases, particularly rabbit carboxylesterase upon administration of CPT-11 (see entire document, particularly pp. 922-923, Figs 1 and 5).

Searle teach recombinant methods in bacteria for enhancing the catalytic efficiency of prodrug activating enzymes, including site-directed mutagenesis (see entire document, particularly pp. 2, 4-9, 11).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced method of treating tumor cells in a patient comprising administering in sequence (i) a non-covalently bound complex comprising a multispecific targeting protein comprising at least one tumor-binding site and one hapten-binding site, and a hapten-enzyme covalent conjugate, (ii) optionally administering a clearing agent, and (iii) administering a prodrug, capable of being converted to a more active drug by the

tumor localized complex for therapeutic benefit in human tumor patients, wherein the enzyme is rat or human carboxylesterase or the enzyme is produced by recombinant techniques in bacteria and is modified by site-directed mutagenesis to enhance its catalytic rate.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced method of treating tumor cells in a patient comprising administering in sequence (i) a non-covalently bound complex comprising a multispecific targeting protein comprising at least one tumor-binding site and one hapten-binding site, and a hapten-enzyme covalent conjugate, (ii) optionally administering a clearing agent, and (iii) administering a prodrug, capable of being converted to a more active drug by the tumor localized complex for therapeutic benefit in human tumor patients, wherein the enzyme is rat or human carboxylesterase or the enzyme is produced by recombinant techniques in bacteria and is modified by site-directed mutagenesis to enhance its catalytic rate in view of Hansen et al [a] and Danks et al and Searle because Hansen et al [a] teach a method of treating target cells in a patient comprising administering a bi-specific antibody or fragment comprising at least one arm that binds a target tissue and at least one other arm that binds a hapten and a hapten-enzyme covalent conjugate comprising at least one hapten, wherein the hapten-enzyme conjugate is mixed with the targeting bi-specific antibody prior to administration (i.e., non-covalently bound complex), optionally administering a clearing agent to clear unbound non-covalent complexes and administering a chemotherapeutic drug or prodrug that

is converted to a more active drug by the pre-targeted enzyme and Danks et al teach antibody-directed enzyme prodrug therapy of tumor cells using rabbit or human carboxylesterase, which effectively inhibit tumor growth upon administration of the prodrug CPT-11 and Searle teach recombinant methods including site-directed mutagenesis for enhancing the catalytic efficiency of prodrug activating enzymes. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to use rabbit or human carboxylesterase in the hapten-enzyme conjugate of Hansen et al [a] or modify the enzyme of the hapten-enzyme conjugate by site-directed mutagenesis to enhance its catalytic rate, thereby increasing the efficiency at which a prodrug is converted to the active drug at the tumor site in the method of Hansen et al [a]. Thus, it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to have produced method of treating tumor cells in a patient comprising administering in sequence (i) a non-covalently bound complex comprising a multispecific targeting protein comprising at least one tumor-binding site and one hapten-binding site, and a hapten-enzyme covalent conjugate, (ii) optionally administering a clearing agent, and (iii) administering a prodrug, capable of being converted to a more active drug by the tumor localized complex for therapeutic benefit in human tumor patients, wherein the enzyme is rat or human carboxylesterase or the enzyme is produced by recombinant techniques in bacteria and is modified by site-directed mutagenesis to enhance its catalytic rate in view of Hansen et al [a] and Danks et al and Searle.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Double Patenting

16. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. Claims 1-3, 5-32 and 34-35 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 16 and 18 of U.S. Patent No. 6,962,702 B2 in view of Hansen et al [a] (WO 99/66951, 12/29/1999) and Basu et al (International Journal of Cancer, 62:472-479, 1995) and Barbet et al (U.S. Patent 5,256,395, issued 10/26/1993) and Haisma et al

(Blood, 92(1):184-190, 1998) and Danks et al (Clinical Cancer research 5:917-924, April 1999) and Searle (WO 00/43541, published 7/27/2000).

The instant claims are drawn to a method of treating target cells in a mammalian or human subject comprising administering in sequence a non-covalently bound complex to said mammalian or human subject thereby forming a target-tissue localized complex, wherein said non-covalently bound complex comprises a multispecific targeting protein comprising at least one target-binding site and one hapten-binding site, and a hapten-enzyme covalent conjugate, wherein said at least one target- binding site binds to the target cells/tissue and wherein said hapten-binding site in non-covalently bound to the hapten-enzyme covalent conjugate, optionally administering a clearing agent, and administering a chemotherapeutic drug or prodrug, capable of being converted to a more active drug by the target-tissue localized complex and the chemotherapeutic prodrug has greater solubility than the active drug produced by the non-covalently bound complex and the prodrug is a prodrug of a camptothecin, doxorubicin, taxol, actinomycin, maytansine, calicheamicin or epithilone class of drug or is the prodrug CPT-11, a prodrug of SN-38. Further, the multispecific targeting protein is a mutlispecific antibody or multispecific antibody fragment, is at least bi-specific, multivalent, is murine, chimeric, humanized or human and binds EGP-1 and the multispecific antibody binds both its antigen and the hapten with a dissociation constant of at least 10^{-7}, more preferably at least $10^{-9,}$ is administered by intravenous injection and the hapten-enzyme comprises at least one hapten, selected from HSG, DTPA, indium-DTPA, DOTA, indium-DOTA,

yttrium-DOTA, fluorescein or biotin and the haptens are linked to the enzyme via a single reaction site by a peptide from 2-10, 2-5 or 3 amino acid residues in length and the enzyme of the hapten-enzyme conjugate is an esterase, amidase, glucuronidase, galactosidase or carboxylesterase, is recombinantly produced in yeast, bacteria, plants, insect cells or animals and is modified by site-directed mutagenesis to increase the rate of enzyme-substrate catalysis and the clearing agent is an anti-idiotypic antibody or a galactosylated anti-idiotypic antibody to the multispecific targeting protein.

Claims 1, 16, and 18 of U.S. Patent No. 6,962,702 B2 are drawn to a method of treating diseased tissues in a subject comprising administering a bi-specific antibody or antibody fragment having at least one arm that specifically binds a targeted tissue and at least one arm that binds a targetable conjugate comprising at least two HSG haptens (i.e., comprises the Fv of monoclonal antibody 679), optionally administering a clearing composition to clear non-localized antibody or antibody fragments from circulation, administering to said subject a targetable conjugate that comprises at least two HSG haptens and a diagnostic or therapeutic agent or enzyme and when said targetable conjugate comprises an enzyme, further administering to said subject a prodrug capable of being converted to a drug at the target site, wherein said at least one arm that specifically binds a targeted tissue is a monoclonal antibody or a fragment of a monoclonal antibody and the targeted tissue is a tumor. Claims 1, 16 and 18 of U.S. Patent No. 6,962,702 B2 do not specifically teach wherein the hapten-enzyme conjugate is mixed with the targeting bi-specific antibody prior to

administration to form a non-covalently bound complex optionally followed by administration of a galactosylated anti-idiotypic antibody (clearing agent) to the bi-specific antibody or antibody fragment or wherein the bi-specific antibody is multivalent, murine, chimeric, humanized, or human, is injected in intravenously, binds EGP-1 and wherein the haptens of the hapten-enzyme conjugate are attached via a single reaction site to the enzyme or are linked by a peptide from about 2-10, 2-5 or 3 amino acid residues in length and wherein the enzyme is an esterase, amidase, glucuronidase, galactosidase or is a carboxylesterase selected from rat, mouse rabbit, porcine or human carboxylesterase, or the enzyme is produced by recombinant techniques in yeast, bacteria, plants, insect cells or animals and is modified by site-directed mutagenesis to increase the rate of catalysis and wherein the bi-specific antibody binds both the target tissue and the hapten with a dissociation constant of at least 10^{-7}, more preferably at least 10^{-9} and wherein the prodrug is a prodrug of camptothecin, doxorubicin, taxol, actinomycin, maytansine, calicheamicin or epithilone class of drug or is the prodrug CPT-11 (i.e., the prodrug of SN-38) or wherein the subject is a human. These deficiencies are made up for in the teachings of Hansen et al [a] and Basu et al and Barbet et al and Haisma et al and Danks et al and Searle.

Hansen et al [a] have been described supra.

Basu et al have been described supra.

Barbet et al have been described supra.

Haisma et al have been described supra.

Danks et al have been described supra.

Searle has been described supra.

The claims in the instant application are obvious variants of claims 1, 16, and 18 of U.S. Patent No. 6,962,702 B2 because it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of claims 1, 16 and 18 of U.S. Patent No. 6,962,702 B2 wherein the hapten-enzyme conjugate is mixed with the targeting bi-specific antibody prior to administration to form a non-covalently bound complex optionally followed by administration of a galactosylated anti-idiotypic antibody (clearing agent) to the bi-specific antibody or antibody fragment and wherein the bi-specific antibody is multivalent, murine, chimeric, humanized, or human, is injected intravenously, binds the tumor-associated antigen EGP-1, has a dissociation constant of at least 10^{-7}, more preferably at least 10^{-9} for both the antigenic target and the hapten, and wherein the haptens of the hapten-enzyme conjugate are attached via a single reaction site to the enzyme or are linked by a peptide from about 2-10, 2-5 or 3 amino acid residues in length and wherein the enzyme is an esterase, amidase, glucuronidase, galactosidase or is a carboxylesterase selected from rat, mouse rabbit, porcine or human carboxylesterase, or the enzyme is produced by recombinant techniques in yeast, bacteria, plants, insect cells or animals and is modified by site-directed mutagenesis to increase the rate of catalysis and wherein the prodrug is a prodrug of camptothecin, doxorubicin, taxol, actinomycin, maytansine, calicheamicin or epithilone class of drug or is the prodrug CPT-11 (i.e., the prodrug of SN-38) and the subject is a human.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to modify the method of claims 1, 16 and 18 of U.S. Patent No. 6,962,702 B2 wherein the hapten-enzyme conjugate is mixed with the targeting bi-specific antibody prior to administration to form a non-covalently bound complex optionally followed by administration of a galactosylated anti-idiotypic antibody (clearing agent) to the bi-specific antibody or antibody fragment and wherein the bi-specific antibody is multivalent, murine, chimeric, humanized, or human, is injected intravenously, binds the tumor-associated antigen EGP-1, has a dissociation constant of at least 10^{-7}, more preferably at least 10^{-9} for both the antigenic target and the hapten, and wherein the haptens of the hapten-enzyme conjugate are attached via a single reaction site to the enzyme or are linked by a peptide from about 2-10, 2-5 or 3 amino acid residues in length and wherein the enzyme is an esterase, amidase, glucuronidase, galactosidase or is a carboxylesterase selected from rat, mouse rabbit, porcine or human carboxylesterase, or the enzyme is produced by recombinant techniques in yeast, bacteria, plants, insect cells or animals and is modified by site-directed mutagenesis to increase the rate of catalysis and wherein the prodrug is a prodrug of camptothecin, doxorubicin, taxol, actinomycin, maytansine, calicheamicin or epithilone class of drug or is the prodrug CPT-11 (i.e., the prodrug of SN-38) and the subject is a human in view of Hansen et al [a] and Basu et al and Barbet et al and Haisma et al and Danks et al and Searle because Hansen et al [a] teach a method of treating a patient comprising administering a bi-specific antibody or fragment having at least one

arm that binds a targeted tissue and at least one other arm that binds a hapten and a hapten-enzyme covalent conjugate comprising at least one hapten, wherein the hapten-enzyme conjugate is mixed with the targeting bi-specific antibody prior to administration (i.e., non-covalently bound complex), optionally administering a galactosylated anti-idiotypic antibody to the bi-specific antibody of the non-covalent complex to clear non-localized non-covalent complexes and administering a chemotherapeutic drug or prodrug that is converted to a more active drug by the pre-targeted enzyme and Hansen et al [a] also teach bi-specific or multispecific antibodies and antigen-binding fragments thereof that are monovalent or divalent and murine, chimeric, humanized and human antibodies and the hapten-enzyme comprises at least one hapten selected from fluorescein, DTPA, indium-DTPA, NOTA, DOTA, indium-DOTA and yttrium-DOTA wherein the haptens are linked by a peptide from 2-10 amino acid residues and the enzyme is a glucuronidase or a carboxylesterase, and various prodrugs including epirubicin, topotecan, maytansinoids, calicheamicins and CPT-11, which is converted by carboxylesterase to the active drug SN-38 that remains in the vicinity of the tumor due to its poor solubility, i.e., the prodrug has a greater aqueous solubility than the active drug produced by the non-covalent complex and Basu et al teach the epithelial glycoprotein-1 (EGP-1) expressed in various human tumors of epithelial origin including breast, bladder, lung, ovary, prostate, pancreas and stomach and Barbet et al teach intravenous injection of multivalent, multispecific antibodies or antigen-binding fragments thereof comprising two or more binding sites, wherein at least one binding site has

affinity towards a hapten moiety (i.e., HSG) and at least one binding site has high affinity towards a tumor-associated antigen and a carrier molecule (affinity enhancement probe) comprising a therapeutic agent and at least two hapten moieties wherein the tumor-associated antigen binding site has a dissociation constant smaller than 10^{-8}M and the hapten binding site has a dissociation constant between 10^{-9}-10^{-7} and Haisma et al teach that chemical conjugation of enzymes in antibody-directed enzyme prodrug therapy results in conjugate heterogeneity due to the lack of specificity of the reagents used for conjugation and necessitates additional purification steps and often results in reduced enzymatic activity or diminished binding activity of the conjugate, whereas recombinantly produced conjugates consist of a uniform product with predictable properties and Danks et al teach antibody-directed enzyme prodrug therapy of tumor cells using rabbit or human carboxylesterase, which effectively inhibit tumor growth upon administration of the prodrug CPT-11 and Searle teach recombinant methods including site-directed mutagenesis for enhancing the catalytic efficiency of prodrug activating enzymes. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of claims 1, 16 and 18 of U.S. Patent No. 6,962,702 B2 wherein the hapten-enzyme conjugate is mixed with the targeting bi-specific antibody prior to administration to form a non-covalently bound complex optionally followed by administration of a galactosylated anti-idiotypic antibody (clearing agent) to the bi-specific antibody or antibody fragment and wherein the bi-specific antibody is multivalent, murine, chimeric, humanized, or human, is

injected intravenously, binds the tumor-associated antigen EGP-1, has a dissociation constant of at least 10^{-7}, more preferably at least 10^{-9} for both the antigenic target and the hapten, and wherein the haptens of the hapten-enzyme conjugate are attached via a single reaction site to the enzyme or are linked by a peptide from about 2-10, 2-5 or 3 amino acid residues in length and wherein the enzyme is an esterase, amidase, glucuronidase, galactosidase or is a carboxylesterase selected from rat, mouse rabbit, porcine or human carboxylesterase, or the enzyme is produced by recombinant techniques in yeast, bacteria, plants, insect cells or animals and is modified by site-directed mutagenesis to increase the rate of catalysis and wherein the prodrug is a prodrug of camptothecin, doxorubicin, taxol, actinomycin, maytansine, calicheamicin or epithilone class of drug or is the prodrug CPT-11 (i.e., the prodrug of SN-38) and the subject is a human in view of Hansen et al [a] and Basu et al and Barbet et al and Haisma et al and Danks et al and Searle.

18. Claims 1-3, 5-32 and 34-35 are directed to an invention not patentably distinct from claims 1, 16 and 18 of commonly assigned U.S. Patent No. 6,962,702 B2. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned U.S. Patent 6,962,702 B2, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not

commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

19. Claims 1-3, 5-32 and 34-35 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 12-18 of copending Application No. 09/337,756 (now allowed) in view of in view of Hansen et al [a] (WO 99/66951, 12/29/1999) and Basu et al (International Journal of Cancer, 62:472-479, 1995) and Barbet et al (U.S. Patent 5,256,395, issued 10/26/1993) and Haisma et al (Blood, 92(1):184-190, 1998) and Danks et al (Clinical Cancer research 5:917-924, April 1999) and Searle (WO 00/43541, published 7/27/2000).

Instant claims 1-3, 5-32 and 34-35 have been described supra.

Claims 1 and 12-18 recite a method of treating diseased tissues in a subject comprising administering a bi-specific antibody or antibody fragment having at least one arm that specifically binds a targeted tissue and at least one

arm that binds a targetable conjugate, optionally administering a clearing composition to clear non-localized antibody or antibody fragments from circulation, administering to said subject a targetable conjugate that comprises a carrier portion and one or more conjugated enzymes, said carrier portion bears at least one hapten recognized by at least one arm of the bi-specific antibody, and administering to said subject a drug or prodrug, wherein said bi-specific antibody is a monoclonal antibody or a fragment of a monoclonal antibody or is humanized and wherein the carrier portion comprises a carbohydrate. Claims 1 and 12-18 of copending Application No. 09/337,756 do not specifically teach wherein the hapten-enzyme conjugate (i.e., targetable conjugate) is mixed with the targeting bi-specific antibody prior to administration to form a non-covalently bound complex optionally followed by administration of a galactosylated anti-idiotypic antibody (clearing agent) to the bi-specific antibody or antibody fragment or wherein the bi-specific antibody is multivalent, murine, chimeric, humanized, or human, is injected in intravenously, binds EGP-1 and wherein the haptens of the hapten-enzyme conjugate are attached via a single reaction site to the enzyme or are linked by a peptide from about 2-10, 2-5 or 3 amino acid residues in length and wherein the enzyme is an esterase, amidase, glucuronidase, galactosidase or is a carboxylesterase selected from rat, mouse rabbit, porcine or human carboxylesterase, or the enzyme is produced by recombinant techniques in yeast, bacteria, plants, insect cells or animals and is modified by site-directed mutagenesis to increase the rate of catalysis and wherein the bi-specific antibody binds both the target tissue and the hapten with a dissociation constant of at

least 10^{-7}, more preferably at least 10^{-9} and wherein the prodrug is a prodrug of camptothecin, doxorubicin, taxol, actinomycin, maytansine, calicheamicin or epithilone class of drug or is the prodrug CPT-11 (i.e., the prodrug of SN-38) or wherein the subject is a human. These deficiencies are made up for in the teachings of Hansen et al [a] and Basu et al and Barbet et al and Haisma et al and Danks et al and Searle.

Hansen et al [a] have been described supra.

Basu et al have been described supra.

Barbet et al have been described supra.

Haisma et al have been described supra.

Danks et al have been described supra.

Searle has been described supra.

The claims in the instant application are obvious variants of claims 1 and 12-18 of copending Application No. 09/337,756 because it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of claims 1 and 12-18 of copending Application No. 09/337,756 wherein the hapten-enzyme conjugate is mixed with the targeting bi-specific antibody prior to administration to form a non-covalently bound complex optionally followed by administration of a galactosylated anti-idiotypic antibody (clearing agent) to the bi-specific antibody or antibody fragment and wherein the bi-specific antibody is multivalent, murine, chimeric, humanized, or human, is injected in intravenously, binds the tumor-associated antigen EGP-1, has a dissociation constant of at least 10^{-7}, more preferably at least 10^{-9} for

both the antigenic target and the hapten, and wherein the haptens of the hapten-enzyme conjugate are attached via a single reaction site to the enzyme or are linked by a peptide from about 2-10, 2-5 or 3 amino acid residues in length and wherein the enzyme is an esterase, amidase, glucuronidase, galactosidase or is a carboxylesterase selected from rat, mouse rabbit, porcine or human carboxylesterase, or the enzyme is produced by recombinant techniques in yeast, bacteria, plants, insect cells or animals and is modified by site-directed mutagenesis to increase the rate of catalysis and wherein the prodrug is a prodrug of camptothecin, doxorubicin, taxol, actinomycin, maytansine, calicheamicin or epithilone class of drug or is the prodrug CPT-11 (i.e., the prodrug of SN-38) and the subject is a human.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to modify the method of claims 1 and 12-18 of copending Application No. 09/337,756 wherein the hapten-enzyme conjugate is mixed with the targeting bi-specific antibody prior to administration to form a non-covalently bound complex optionally followed by administration of a galactosylated anti-idiotypic antibody (clearing agent) to the bi-specific antibody or antibody fragment and wherein the bi-specific antibody is multivalent, murine, chimeric, humanized, or human, is injected in intravenously, binds the tumor-associated antigen EGP-1, has a dissociation constant of at least 10^{-7}, more preferably at least 10^{-9} for both the antigenic target and the hapten, and wherein the haptens of the hapten-enzyme conjugate are attached via a single reaction site to the enzyme or are linked by a

peptide from about 2-10, 2-5 or 3 amino acid residues in length and wherein the enzyme is an esterase, amidase, glucuronidase, galactosidase or is a carboxylesterase selected from rat, mouse rabbit, porcine or human carboxylesterase, or the enzyme is produced by recombinant techniques in yeast, bacteria, plants, insect cells or animals and is modified by site-directed mutagenesis to increase the rate of catalysis and wherein the prodrug is a prodrug of camptothecin, doxorubicin, taxol, actinomycin, maytansine, calicheamicin or epithilone class of drug or is the prodrug CPT-11 (i.e., the prodrug of SN-38) and the subject is a human in view of Hansen et al [a] and Basu et al and Barbet et al and Haisma et al and Danks et al and Searle because Hansen et al [a] teach a method of treating a patient comprising administering a bi-specific antibody or fragment having at least one arm that binds a targeted tissue and at least one other arm that binds a hapten and a hapten-enzyme covalent conjugate comprising at least one hapten, wherein the hapten-enzyme conjugate is mixed with the targeting bi-specific antibody prior to administration (i.e., non-covalently bound complex), optionally administering a galactosylated anti-idiotypic antibody to the bi-specific antibody of the non-covalent complex to clear non-localized non-covalent complexes and administering a chemotherapeutic drug or prodrug that is converted to a more active drug by the pre-targeted enzyme and Hansen et al [a] also teach bi-specific or multispecific antibodies and antigen-binding fragments thereof that are monovalent or divalent and murine, chimeric, humanized and human antibodies and the hapten-enzyme comprises at least one hapten selected from fluorescein, DTPA, indium-DTPA,

NOTA, DOTA, indium-DOTA and yttrium-DOTA wherein the haptens are linked by a peptide from 2-10 amino acid residues and the enzyme is a glucuronidase or a carboxylesterase, and various prodrugs including epirubicin, topotecan, maytansinoids, calicheamicins and CPT-11, which is converted by carboxylesterase to the active drug SN-38 that remains in the vicinity of the tumor due to its poor solubility, i.e., the prodrug has a greater aqueous solubility than the active drug produced by the non-covalent complex and Basu et al teach the epithelial glycoprotein-1 (EGP-1) expressed in various human tumors of epithelial origin including breast, bladder, lung, ovary, prostate, pancreas and stomach and Barbet et al teach intravenous injection of a multivalent, multispecific antibodies or antigen-binding fragments thereof comprising two or more binding sites, wherein at least one binding site has affinity towards a hapten moiety (i.e., HSG) and at least one binding site has high affinity towards a tumor-associated antigen and a carrier molecule (affinity enhancement probe) comprising a therapeutic agent and at least two hapten moieties wherein the tumor-associated antigen binding site has a dissociation constant smaller than 10^{-8}M and the hapten binding site has a dissociation constant between 10^{-9}-10^{-7} and Haisma et al teach that chemical conjugation of enzymes in antibody-directed enzyme prodrug therapy results in conjugate heterogeneity due to the lack of specificity of the reagents used for conjugation and necessitates additional purification steps and often results in reduced enzymatic activity or diminished binding activity of the conjugate, whereas recombinantly produced conjugates consist of a uniform product with predictable properties and Danks et

al teach antibody-directed enzyme prodrug therapy of tumor cells using rabbit or human carboxylesterase, which effectively inhibit tumor growth upon administration of the prodrug CPT-11 and Searle teach recombinant methods including site-directed mutagenesis for enhancing the catalytic efficiency of prodrug activating enzymes. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of claims 1 and 12-18 of copending Application No. 09/337,756 wherein the hapten-enzyme conjugate is mixed with the targeting bi-specific antibody prior to administration to form a non-covalently bound complex optionally followed by administration of a galactosylated anti-idiotypic antibody (clearing agent) to the bi-specific antibody or antibody fragment and wherein the bi-specific antibody is multivalent, murine, chimeric, humanized, or human, is injected in intravenously, binds the tumor-associated antigen EGP-1, has a dissociation constant of at least 10^{-7}, more preferably at least 10^{-9} for both the antigenic target and the hapten, and wherein the haptens of the hapten-enzyme conjugate are attached via a single reaction site to the enzyme or are linked by a peptide from about 2-10, 2-5 or 3 amino acid residues in length and wherein the enzyme is an esterase, amidase, glucuronidase, galactosidase or is a carboxylesterase selected from rat, mouse rabbit, porcine or human carboxylesterase, or the enzyme is produced by recombinant techniques in yeast, bacteria, plants, insect cells or animals and is modified by site-directed mutagenesis to increase the rate of catalysis and wherein the prodrug is a prodrug of camptothecin, doxorubicin, taxol, actinomycin, maytansine, calicheamicin or epithilone class of drug or is the

prodrug CPT-11 (i.e., the prodrug of SN-38) and the subject is a human in view of Hansen et al [a] and Basu et al and Barbet et al and Haisma et al and Danks et al and Searle.

This is a provisional obviousness-type double patenting rejection, however, it is noted that copending application No. 09/337,756 is now allowed.

20. Claims 1-3, 5-32 and 34-35 are directed to an invention not patentably distinct from claims 1 and 12-18 of commonly assigned copending Application No. 09/337,756. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned copending Application No. 09/337,756, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C.

102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Conclusion

21. No claim is allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

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Respectfully,
David J. Blanchard
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